

Supplementary Table 1. Clinical data from patients for all 25 autopsy samples, color-coded for those with a *SOD1* mutation in purple, sALS patients in blue, patients with a *C9orf72* expansion in green, and control patients without ALS in black font. Average microglia score is the average rank from 3 independent observers, blinded to genotype, on a scale of 0-3.

| Average Microglia Score | Diagnosis | Site of symptom onset | Disease duration (years) | Identified ALS-relevant genetic mutation | <i>SOD1</i> | <i>TARDBP</i> | <i>C9orf72</i> | <i>UBQLN2</i> |
|-------------------------|---------------|-----------------------|--------------------------|--|-------------|---------------|----------------|---------------|
| 3 | possible ALS | lumbosacral | 1 | <i>SOD1</i> ^{A4V} | A4V | Negative | Absent | Negative |
| 3 | suspected ALS | lumbosacral | 2 | <i>SOD1</i> ^{A4T} | A4T | Negative | Absent | Negative |
| 3 | probable ALS | cervical | 2 | none | | Negative (E6) | Absent | Negative |
| 2.53 | definite ALS | cervical | 2 | none | | Negative | Absent | Negative |
| 2.47 | none | n/a | n/a | <i>SOD1</i> ^{A4V} | A4V | | | |
| 2.25 | suspected ALS | bulbar | 3 | <i>C9orf72</i> | Negative | Negative | Expansion | Negative |
| 1.92 | probable ALS | lumbosacral | 6 | <i>SOD1</i> ^{D125V} | D125V | Negative | Absent | Negative |
| 1.67 | definite ALS | bulbar | 1 | Risk factor (ATXN2 29) | Negative | Negative (E6) | Absent | Negative |
| 1.5 | definite ALS | cervical | 2 | none | | Negative | Absent | Negative |
| 1.5 | definite ALS | cervical | 3 | none | | Negative | Absent | Negative |
| 1.39 | none | n/a | n/a | none | | | Absent | |
| 1.36 | probable ALS | lumbosacral | 5 | <i>C9orf72</i> | Negative | Negative | Expansion | Negative |
| 1.33 | probable ALS | bulbar | 3 | <i>C9orf72</i> | Negative | Negative | Expansion | Negative |
| 1.33 | probable ALS | lumbar | 4 | none | | | Absent | |
| 1.28 | none | n/a | n/a | none | | | Absent | |
| 1 | none | n/a | n/a | none | | | Absent | |
| 0.67 | none | n/a | n/a | none | | | Absent | |
| 0.67 | probable ALS | lumbosacral | 1 | <i>C9orf72</i> | Negative | Negative | Expansion | Negative |
| 0.5 | possible ALS | lumbosacral | 1 | <i>C9orf72</i> | Negative | Negative | Expansion | Negative |
| 0.25 | definite ALS | cervical | 1 | none | | Negative (E6) | Absent | Negative |
| 0.17 | probable ALS | lumbosacral | 3 | Risk factor (ATXN2 31) | Negative | Negative | Absent | Negative |
| 0.17 | none | n/a | n/a | none | | | Absent | |
| 0.13 | definite ALS | lumbar | 5 | none | | Negative (E6) | Absent | Negative |
| 0 | probable ALS | lumbar | 4 | none | | Negative | Absent | Negative |
| 0 | Suspected ALS | bulbar | 2 | <i>C9orf72</i> | Negative | Negative | Expansion | Negative |

Microglia score: 0, absent; 1, mild density; 2, moderate density; 3, high density; n/a: not applicable

Supplementary Table 2: Amount of microglial depletion affects various recovery parameters including: hTDP-43 clearance, maximum CMAP recorded from the gastrocnemius muscle, MN loss, and TA denervation

| Animal # | Treatment | Microglia density (per mm ²) | Avg hTDP-43 per MN (a.u.) | Max. evoked CMAP (mV) | Avg # lumbar MNs per ventral horn | % intact TA NMJs |
|----------|--------------|---|------------------------------|--------------------------|--------------------------------------|---------------------|
| 5545 | PLX3397 | 13.9 | 1147 | 7.2 | 16.9 | 42.1 |
| 5529 | PLX3397 | 54.6 | 864 | 8.8 | 17.5 | NA |
| 5479 | PLX3397 | 70.8 | 725 | 9.1 | 17.1 | 44.3 |
| 5480 | PLX3397 | 92.5 | 715 | 10.1 | 17.2 | 59.2 |
| 5557 | PLX3397 | 113.2 | 696 | 12.4 | 17.9 | 45.3 |
| 5512 | Nutella only | 158.8 | 433 | 9.3 | 20.2 | 63.3 |
| 5556 | Nutella only | 160.8 | 423 | 15.5 | 19.3 | 63.8 |
| 5509 | Nutella only | 161.9 | 534 | 12.7 | 20.4 | 54.9 |
| 5474 | Nutella only | 168.1 | 552 | 11.9 | 19.9 | 62 |
| 5449 | Nutella only | 176.5 | 657 | 13.3 | 19.3 | 66.4 |